REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-61 are pending.

The amendments are supported by the original disclosure and, thus, no new matter has been added. For example, new claims 41-45 are similar to present claims 1-5 except for recitation of a detection limit. New claims 46-57 are similar to claims 8-22. Support for new claims 58-59 and 61 can be found on page 8, top paragraph, of the specification ("The subject assay can detect DNA larger than 100 base pairs regardless of base sequence or species of DNA"). New claim 60 is supported by page 11 of the specification.

After receipt of this final Office Action, the undersigned contacted the Examiner to ask for finality to be withdrawn under M.P.E.P. § 706.07(d) because it was premature. In the Office Action, the Examiner asserts "All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and **could have been finally rejected on the grounds** and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR. 1.114" (page 5, emphasis added). Applicants urge that final rejection in the first Office Action is improper since the Action contains **two new grounds of rejections** that were not of record in the previous application. Thus, finality is improper and should be withdrawn.

More specifically, in the Preliminary Amendment filed May 15, 2002, each of the independent claims were amended to recite the step of "determining whether the total nucleic acid in said sample is higher or lower than a threshold amount of contamination, wherein the threshold amount of contamination is equal to or less than 100 pg" (see, for example, step (g) of claim 1). In the Office Action mailed July 30, 2002, the Examiner issued new rejections under the first and second paragraphs of 35 U.S.C. § 112 based on this new limitation and made the rejections final. As stated in the M.P.E.P.,

> "Before final rejection is in order a clear issue should be developed between the examiner and applicant . . . the goal of reaching a clearly defined issue for an early termination, i.e., either an allowance of the application **or a final rejection** . . . While the rules no longer give to an applicant the right to "amend as often as the examiner presents new references or reasons for rejection," **present practice does not sanction hasty and ill-considered**

> **final rejections**. The applicant who is seeking to define his or her invention in the claims that will give him or her the patent protection to which he or she is justly entitled should receive the cooperation of the examiner to that end, and not be prematurely cut off in the prosecution of his or her application . . . The examiner should never lose sight of the fact that in every case the applicant is entitled to a full and fair hearing, and **that a clear issue between applicant and examiner should be developed**, if possible, before appeal.

[§ 706.07, emphasis added].

Since the new grounds of rejection were not of record in the previous application, Applicants respectfully submit that it is improper to issue a final rejection in a first Office Action here. Moreover, the amendments clearly raise "new issues" since they resulted in new rejections not of record in the previous application. Therefore, Applicants request that the finality of this Office Action be withdrawn.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 1-40 were rejected under Section 112, first paragraph, because it was alleged that they contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." Applicants traverse because the challenged limitation (i.e., "the threshold amount of contamination") is supported by the original disclosure of the invention.

The present claims are fully supported by the specification as originally filed in compliance with Section 112, first paragraph. A person of ordinary skill in the art would recognize that this limitation is supported by the original disclosure of the invention as described in the present specification. The specification clearly states:

> The primary concern of regulatory agencies is the potential contamination of product with oncogenes and infectious viral DNA. . . . Because the risk associated with exposure of 100 pg of DNA per dose is negligible, the WHO (World Health Organization) currently requires the DNA in all biopharmaceuticals to be below 100 pg per dose. Thus, methodologies that accurately determine picogram amounts of DNA have become a requisite in the biopharmaceutical field. Several different methodologies exist for quantitation of DNA. Each method has limitations with respect to dynamic range for accurate DNA quantitation and biases due to base composition.

[page 2].

The specification also specifically states that the "present invention relates to a method for the determination of the presence and amount of DNA in a sample" (page 1). Applicants urge that in view of the disclosure in the specification as filed, a person of ordinary skill in the art would recognize that the WHO has established a threshold value for the total DNA contamination of the sample which divides the acceptable and unacceptable levels and that the instant invention is concerned with improved methods for reliably measuring the DNA levels below this established threshold value of DNA contamination. Indeed, Example 5 of the present specification demonstrates the successful detection of 5 pg of the contaminating DNA in the sample, which is 20-fold lower than the WHO threshold level (see also, Examples 2 and 9).

The subject matter of a claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement of Section 112, first paragraph (M.P.E.P. § 2163.02). Applicants submit that while the term "threshold" is only used in Example 10 (see Table at page 21), absent a requirement for literal support, the inherent support in the specification is sufficient to satisfy the requirements of Section 112, first paragraph. Finally, the Examiner is reminded that the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those of ordinary skill in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d at 1117. Applicants urge that a person of ordinary skill in the art would recognize from the original disclosure in the specification that Applicants were in possession of the instant invention at the time the application was filed. Namely, Applicants were in possession of an assay method for measuring total nucleic acid in the

sample and determining whether or not the sample was free of nucleic acid contamination at the 100 pg threshold level established by the WHO.

Accordingly, Applicants urge that the rejection under Section 112, first paragraph, is improper and should be withdrawn.

35 U.S.C. 112 – Definiteness

Claims 1-40 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The Examiner alleges in the Office Action that "it is unclear what is the definition regarding the language 'a threshold amount of contamination' in the specification" and "it is unclear what is meant by 'the threshold amount of contamination is equal to or less than 100 pg'" (Office Action, page 3). Applicants submit that the limitation objected to by the Examiner is clear and definite to one of ordinary skill in the art when properly construed in view of the specification.

Applicants submit that a fundamental principle contained in Section 112, second paragraph, is that Applicants can be their own lexicographers. Terms in patent claims are not too vague unless they prevent one skilled in the art from understanding, in light of the specification, what is claimed. *Andrew Corp. v. Gabriel Electronics, Inc.*, 6 USPQ2d 2010, 2013 (Fed. Cir. 1988); *U.S. v. Telectronics Inc.*, 8 USPQ2d 1217, 1220 (Fed. Cir. 1988); *Specialty Composites v. Cabot Corp.*, 6 USPQ2d 1601, 1604 (Fed. Cir. 1988). Thus, in the claims, Applicants can define what they regard as their invention essentially in whatever terms they choose as long as the terms are not used contrary to accepted meanings in the art. Applicants may use functional language, alternative expressions, negative limitations, or any style of expression or format of a claim which makes clear the boundaries of the subject matter for which protection is sought (M.P.E.P. § 2173.01).

A claim cannot be rejected solely because of the language used to define the subject matter for which patent protection is sought. *In re Swinehart*, 160 USPQ 226 (CCPA 1971). The focus in determining compliance with Section 112, second para-

graph, should be whether the claims meet the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available. (M.P.E.P. § 2173.02).

Therefore, Applicants urge that this rejection is improper and should be withdrawn.

In any case, Applicants urge the claims are sufficiently clear and definite to one of ordinary skill in the art when properly construed in view of the specification and what is known in the art. (see M.P.E.P. § 2173). One of ordinary skill in the art would readily understand the meaning of the terms "a threshold amount of contamination" and "the threshold amount of contamination is equal to or less than 100 pg" as used in the claims (see claim 1) when properly construed in view of the specification. One of ordinary skill in the art would understand that the methods distinguish samples having a level of contamination below the threshold amount from samples having levels of contamination above the threshold. It would also be understood that the assay must be sufficiently sensitive so that this threshold value can be set at 100 pg (e.g., the WHO requirement) or less (e.g., the 5 pg detection limit from Example 5). One of ordinary skill in the art would be familiar with such terminology and familiar with defining assay sensitivity in the terms of total detectable amount of analyte (e.g., 100 pg) independently of the sample volume. The M.P.E.P. clearly states:

> [The Examiner] should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire.
>
> In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. See, e.g., *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). See also *In re Larsen*, No. 01-1092 (Fed. Cir. May 9, 2001) (unpublished)

[M.P.E.P. § 2173.02].

Applicants maintain that the rejection is improper for the reasons set forth above. Accordingly, Applicants request that the rejection under Section 112, second paragraph, be withdrawn because the pending claims are clear and definite.

35 U.S.C. 103 – Nonobviousness

Claims 1-3, 6-12, 14-25, 28-32 and 34-37 were rejected under Section 103(a) as allegedly being unpatentable over Hartley (U.S. Patent 5,043,272) in view of Eberle et al. (U.S. Patent 5,413,906). Further, claims 4-5, 13, 26-27, 33 and 39-40 were rejected under Section 103(a) as allegedly being unpatentable over Hartley et al. (U.S. Patent 5,043,272) in view of Wu et al. (Genomics, 4:560-569, 1989) and Respess (U.S. Patent 5,599,662). And claim 38 was rejected under Section 103(a) as allegedly being unpatentable over Hartley (U.S. Patent 5,043,272) in view of Kozlowski et al. (U.S. Patent 6,096,499). Applicants traverse and address these rejections collectively.

In the Office Action, the Examiner asserts, "Hartley discloses that the method might be desirable in the quantification of amplification products (See column 8, lines 39-43)" (page 4).

Applicants urge that contrary to the Examiner's assertion, Hartley does not teach or suggest such desirability. Hartley in column 8, lines 39-43 teaches kits which "contain in addition to the reagent listed above, a probe for detecting the papiloma virus" (col.8, lines 45-46). Nothing in the disclosure of Hartley teaches or suggests that this probe can be used for the quantification of the **total amount** of the nucleic acid contamination in the sample. Instead, Hartley is clearly directed to measuring the amount of a specific nucleic acid, not total nucleic acid.

In the Office Action, the Examiner also asserts, "The disclosure of Hartley indicates that very low level DNA is quantified, for example, 100pg of linear HPV 18 DNA was used (. . .) and 10 femtograms of HPV 16 DNA could be tested (. . .)" (page 4).

Applicants urge the Examiner that claims 1-3, 6-12, 14-25 and 34-37 claim a method for measuring **total** nucleic acid in the sample. The fact that low starting levels of specific DNA (HPV 18 and HPV 16), such as 100 pg, may be amplified by the method of Hartley does not teach or suggest the claimed invention and therefore is not sufficient

for a Section 103 rejection. A method that is shown to amplify low levels of the specific DNA in a sample cannot be considered a good predictor for the success in the amplification of the **total** contaminating DNA molecules. Hartley fails to teach or suggest how the amount of total DNA in the sample can be measured at the detection threshold of the instant invention, e.g., 100 pg. Furthermore, the reference fails to teach or suggest the quantitative detection of two or more distinct nucleic acid species of unknown sequence, wherein each of the species is longer than 100 bases.

Moreover, the method for measuring total nucleic acid in the sample would not have been obvious to the person having ordinary skill in the art from the disclosure of Hartley since the reference fails to provide a reasonable expectation of success with respect to the claimed subject matter.

Furthermore, contrary to the Examiner's assertion, Hartley teaches away from the present invention by explicitly teaching the identification and detection of the specific sequences (see, for example, column 8, lines 6-9).

The M.P.E.P. clearly states that the prior art must teach or suggest invention as a whole:

> Ascertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole.
>
> In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences **themselves** would have been obvious, but whether the claimed invention **as a whole** would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983). . . .
>
> The court held "due to the admitted unobviousness of the first two steps of the claimed combination of steps, the subject matter **as a whole** would not have been obvious to one of ordinary skill in the art at the time the invention was made." 535 F.2d at 69, 190 USPQ at 17.

[§ 2141.02]

Applicants maintain that the disclosure of Hartley misses the essential elements of the pending claims and therefore does not teach or suggest every element of the currently pending claims and does not teach the present invention as a whole. Hartley

suggests derivatizing primers with biotin or attaching oligonucleotides to the capture beads exclusively to improve the detection of the specific nucleotide sequences (e.g., HPV 16 DNA was detected using capture beads according to cols. 12 and 13, Table II). Hartley does not teach or suggest how to use biotin-derivatized primers or capture beads to measure the amount of <u>total</u> nucleic acid in the sample.

Therefore, Hartley does not teach or suggest the subject matter defined by currently pending claims 1-3, 6-12, 14-25 and 34-37.

The Examiner further alleges that "one of an ordinary skill in the art . . . would have been motivated to apply the method of Hartley combining the teachings of Eberle et al. to determine the total nucleic acid in a sample with reasonable a expectations of success because the method of Hartley is sensitive enough to be used" (Office Action, page 4).

Applicants submit that Eberle does not compensate for the deficiencies of Hartley. In fact, Eberle teaches away from the present invention. Unlike measuring the total nucleic acid in the sample in a sequence independent manner, Eberle discloses a highly selective detection method:

> The method is highly specific since only immobilized nucleotides and nucleic acids containing the latter are bound to the solid phase. Samples with a less-than-maximum degree of purity are, hence, also acceptable for the method of the invention. Even determination in the presence of bacteria is, for example, possible.

[column 7, lines 3-9].

Contrary to the instant invention directed to measuring the amount of total contaminating DNA, the invention of Eberle teaches detection of highly specific sequences of interest with no sensitivity for contaminating nucleic acids. As specifically stated in the citation above, the bacterial DNA would not be amplified by the method of Eberle.

Therefore, neither the teachings of Eberle nor the teachings of Hartley teach or suggest measuring total nucleic acid concentration in a sample with a mixed starting material.

Applicants further urge that there is no suggestion or motivation to combine the teachings of Hartley et al. with the teachings of Eberle. Therefore, the Examiner fails to provide the required factual support to establish a *prima facie* case of obviousness. The suggestion to combine the elements must come from a prior art and not from the applicant's disclosure. See *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). To establish a *prima facie* obviousness based on combination of references, the Examiner is required to demonstrate that the prior art provide "a reason, suggestion, or motivation to lead an inventor to combine those references." *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

> [E]vidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or in some cases, from nature of the problem solved. . . . The range of sources available, however, **does not diminish the requirements for actual evidence. That is, the showing must be clear and particular**.

In re Dembiczak, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (citation omitted, emphasis added).

Similarly, there is no suggestion or motivation to combine the teachings of Hartley with Wu et al., Respess and/or Kozlowski et al. The combined references fail to compensate for the deficiencies of Hartley.

Wu et al. merely teaches a method for sequence specific nucleic acid amplification. The reference does not teach or suggest that a sensitivity level of 100 pg is achievable with the method of Wu et al. The reference also does not teach or suggest the amplification of the total contaminating DNA in a sample. On the contrary, the reference specifically states:

> We have previously demonstrated that a single base pair mismatch between the template and the substrate oligonucleotides reduces the efficiency of ligating the octamer and tetradecamer substrate pairs. When a hexamer is used instead of the octamer as the 3' substrate, enzyme discrimination of the matched and mismatched base pair is even more pronounced.

[Wu et al., page 563]

Applicants maintain that a person of ordinary skill in the art would not have a reasonable expectation of success in amplifying the total contaminating DNA in the

sample based on the disclosure of Wu et al. By teaching the strong dependence of the amplification efficiency on the exact primer – template match, Wu et al. teaches away from the present invention. Furthermore, absent a suggestion or teaching in the prior art to make the combination proposed by the Examiner, this rejection is improper and should be withdrawn.

The Examiner does not cite any specific teaching or suggestion of Respess in her Office Action which is an aspect of the claimed invention. Therefore, it does not compensate for the deficiencies of Hartley, Eberle and Wu et al. discussed above. Respess merely provides sequences of improved primers for the PCR amplification of one highly specific nucleic acid sequence of a pol gene from HIV-1. The reference does not teach or suggest amplifying total contaminating DNA in a sample. Neither does the reference teach or suggest the sensitivity limit for a quantitative detection of contaminating DNA on the order of 100 pg. Finally, absent a suggestion or teaching in the prior art to make the combination proposed by the Examiner, the rejection is improper and should be withdrawn.

Kozlowski et al. also does not compensate for the deficiencies of Hartley. Absent a suggestion or teaching in the prior art to make the combination proposed by the Examiner, the rejection is improper and should be withdrawn. Furthermore, Kozlowski et al. merely teaches screening for modulators of the primase activity and does not teach the amplification of the total contaminating DNA in the sample with the sensitivity limit on the order of 100 pg. The Examiner does not cite any specific teaching or suggestion of Kozlowski et al. in her Office Action which is an aspect of the claimed invention.

Applicants maintain that Hartley (U.S. Patent No. 5,043,272) alone or in combination with Eberle (U.S. Patent No. 5, 413, 906), Wu et al. (Genomics 4:560-569, 1989), Respess (U.S. Patent No. 5,599,662) and Kozlowski et al. (U.S. Patent No. 6,096,499) does not teach or suggest the presently claimed subject matter.

Finally, the newly added claims are not obvious over the cited prior art. The prior art does not teach or suggest detecting the level of the total DNA contamination of a sample, especially where the sample consists of two or more unique nucleic acid species of unknown sequence. More particularly, it does not teach or suggest that the

contamination contains both DNA and RNA species and each of the species is larger than 100 bases.

Withdrawal of the Section 103 rejection is requested because the invention as claimed would not have been obvious to a person of ordinary skill in the art at the time it was made.

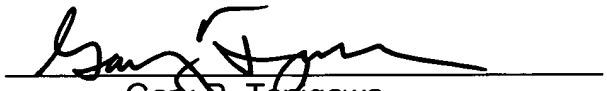
Conclusion

Having fully responded to all of the pending objections and rejections contained in the Office Action (Paper No. 22), Applicants believe the present application to be in condition for allowance or in better condition for an appeal. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Moreover, Applicants believe that an interview would be helpful in addressing any issue which was not successfully traversed or overcome by this Response. Thus, Applicants respectfully request an interview with the Examiner once this Response has been reviewed.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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APPENDIX
MARKED-UP VERSION TO SHOW CHANGES

IN THE CLAIMS

The claims are amended as follows.

15. (3x Amended) A method as in claim 14, wherein said at least one detectable species is selected from the group consisting of biotin, nucleic acid sequence, nucleic acid base pairing linear polymer, fluorescent molecule, electrochemiluminescent molecule, radioactive molecule, peroxidase and alkaline phosphatase.

Claims 41-61 are added as new claims.